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A Magnetoclick Imidazolidinone Nanocatalyst for Asymmetric 1,3-Dipolar Cycloadditions

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Abstract: A 1,3-dipolar azide–alkyne cycloaddition has been used to prepare a magnetic nanoparticle immobilized MacMillan catalyst that catalyzes the enantioselective 1,3-dipolar cycloaddition between nitrones and α,β-unsaturated aldehydes. The catalyst can be recovered and recycled for five consecutive runs without any significant loss in yields and diastereo- and enantioselectivities of the isoxazolidines.

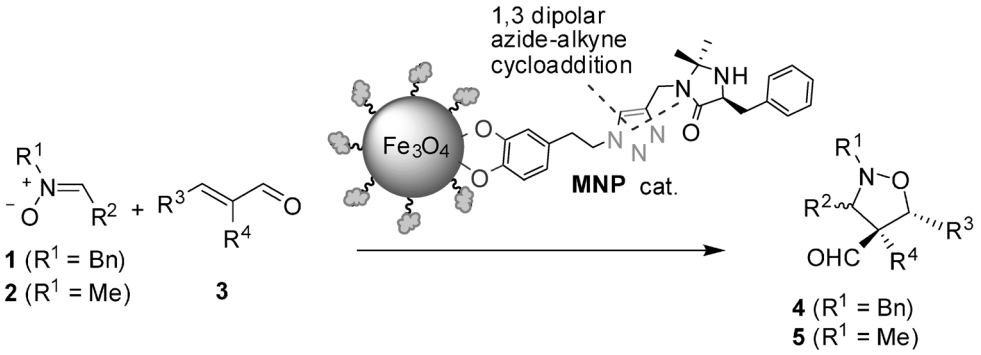
Keywords: asymmetric catalysis; click chemistry; 1,3-dipolar cycloaddition; enantioselectivity; green chemistry; magnetic separation; nano catalyst

Heterogeneous organocatalysts are emerging as powerful tools for asymmetric catalysis because of their potential advantages over homogeneous catalysts, such as efficient activity, ease in recovery and potential reusability.[1,2] The immobilization of organocatalysts is important for the large-scale production of chiral compounds, which are abundant as biologically active molecules and drugs. The key challenges for heterogeneous organocatalysts are to develop cost-effective strategies for immobilization and to use easily recoverable supports which can help to overcome the problems of mechanical loss of the support during recycling experiments. Furthermore, the supported catalyst should be catalytically comparable or superior to its homogeneous counterpart and easily recovered and reused many times with unchanged activity and selectivity.[2]

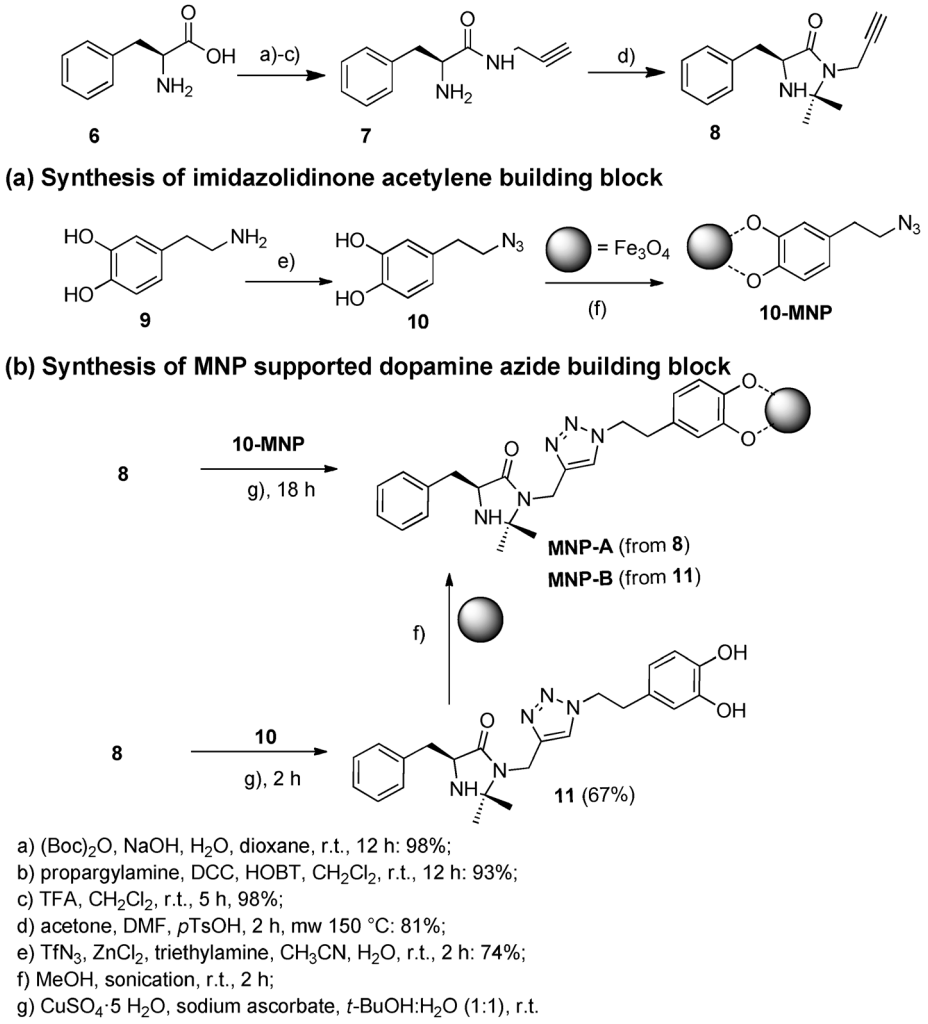
Magnetic nanoparticles (MNPs) have recently emerged as sustainable catalyst supports[3–5] owing to their easy functionalization and synthesis, low toxicity, large surface area, facile separation *via* magnetic force with high dispersion property in organic solvents. Therefore, the development of an easy and straightforward strategy for immobilization of organocatalysts on magnetic nanosupports may facilitate the use of organocatalytic processes for industrial applications.

The chiral MacMillan imidazolidinone is an efficient and versatile organocatalyst for enantioselective reactions involving α,β-unsaturated aldehydes such as the Diels–Alder reaction,[6] 1,3-dipolar cycloaddition,[7] Friedel–Crafts-type alkylation,[8,9] and other organocatalytic processes.[10] Given its importance and efficiency, it has been heterogenized in some ways and used for Diels–Alder reactions[5a,11] and Friedel–Crafts alkylations.[5b,12] We envisaged that the development of an easily synthesizable, inexpensive, recyclable and stereochemically efficient imidazolidinone catalyst still has to be realized for the 1,3-dipolar cycloaddition[13] which is a very useful method in organic synthesis.[14] Herein we report the design and synthesis of a new magnetic nanoparticle functionalized chiral imidazolidinone catalyst using 1,3-dipolar azide–alkyne cycloaddition which catalyzes the 1,3-dipolar cycloaddition of nitrones **1** and **2** with α,β-unsaturated aldehydes **3** to provide isoxazolidines **4** and **5** in a highly stereoselective manner (Scheme 1).

In the course of our investigations into applications of MacMillan's imidazolidinone-based catalyst,[15] the design of a multifunctional prolinamide using "click chemistry"[16] and a recyclable magnetic nanocatalyst,[17] we became interested to design a novel magnetically recoverable imidazolidinone catalyst using the azide–alkyne cycloaddition. The MNPs supported imidazolidinone catalyst has been prepared *via* two strategies using "click chemistry"[18] as shown in Scheme 2. In our synthesis we have efficiently accessed an imidazolidinone alkyne building block **8** in four steps in 72% overall yield from L-phenylalanine **6**. The Boc protection of L-phenylalanine **6** followed by coupling with propargylamine, and subsequent removal of the Boc group afforded the amide derivative **7**. The amide **7** readily underwent microwave-promoted cyclization with acetone in DMF using a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) to afford



Scheme 1. Heterogeneous organocatalytic 1,3-dipolar nitrone cycloaddition.



Scheme 2. Synthesis of functional iron nanoparticles.

the imidazolidinone **8** in 81% yield. The dopamine azide **10** was prepared from dopamine **9**, which was then grafted onto Fe_3O_4 MNPs by ultrasonication. Magnetite nanoparticles (MNPs) used for this work were easily prepared *via* the co-precipitation technique (see the Supporting Information). The MNP supported dopamine azide **10-MNP** was treated with the imidazolidinone-containing alkyne **8** in the presence of Na-ascorbate and $CuSO_4 \cdot 5H_2O$ in *t*-BuOH/H_2O (1:1) as solvent to afford **MNP-A** with 0.10 mmol g^{-1} loading. The loading was determined from elemental analysis. The catalyst **MNP-A** was iso-

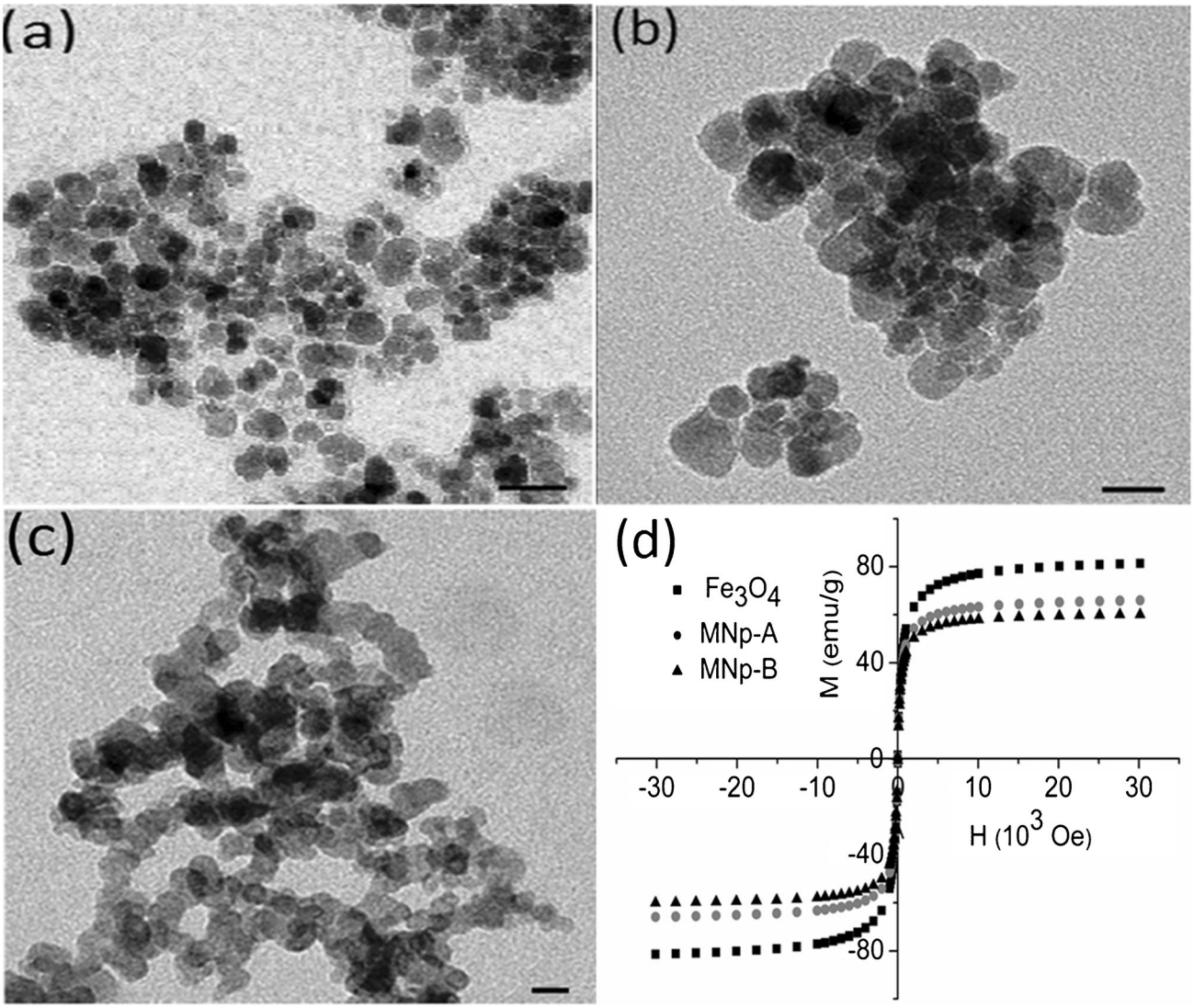


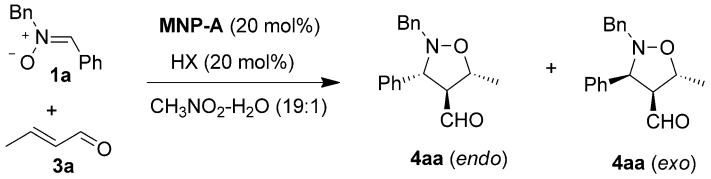
Figure 1. (a) TEM image of Fe_3O_4 MNPs; (b) TEM image of **MNP-A**; (c) TEM image of recovered **MNP-A** after 5 cycles; scale bar 20 nm. (d) Magnetization curves for **MNP-A** and **MNP-B** measured at 300 K.

lated by magnetic decantation and washed with methanol and dicholoromethane several times. The incorporation of azide functional groups onto the **MNP** was confirmed by FT-IR analysis (Supporting Information, Figure S1). For a comparison, the homogeneous imidazolidinone catalyst **11** was prepared from imidazolidinone **8** and dopamine azide **10** in 67% yield. Immobilization of **11** on Fe_3O_4 MNPs was further carried out by ultrasonicating a mixture of **11** and Fe_3O_4 MNPs in methanol at room temperature for 2 h. The MNP supported catalyst **MNP-B** was obtained with 0.14 mmol g^{-1} loading of the chiral imidazolidinone **11** determined from ^{1}H NMR analysis and elemental analysis.

The average sizes of heterogeneous organocatalysts **MNP-A** and **MNP-B** were determined using transmission electron microscopy (TEM) analysis. The TEM images revealed that both **A** and **B** preserved the spherical nanometer dimensions of Fe_3O_4 MNPs. The average diameter is 12 nm for **MNP-A** and **MNP-B**, while the average diameter is 11 nm for Fe_3O_4 MNPs (Figure 1a–c, Supporting Information, Figure S4 and Figure S5). Magnetization curves measured at room temperature showed that MNPs functionalized with imidazolidinone are superparamagnetic (Figure 1d). **MNP-A** and **MNP-B** possessed a saturation magnetization (σ_s) of 65.5 and 60.5 emu g^{-1}, respectively (T = 300 K), which are a little lower than that of the synthesized Fe_3O_4-NPs (81.8 emu g^{-1}). The functionalized MNPs are highly stable and easily dispersible in water and a range of organic solvents.

We next examined the 1,3-dipolar cycloaddition between *N*-benzylidenebenzylamine *N*-oxide (**1a**) with crotonaldehyde (**3a**) using 20 mol% functional magnetic nanocatalyst **MNP-A** as shown in Table 1. The cycloaddition was performed in nitromethane-water

Table 1. Optimization of reaction conditions for 1,3-dipolar cycloaddition using different Brønsted acids.[a]



Entry	HX	Temperature	Time [h]	Conversion[b] [%]	*dr* **4aa** *endo*:*exo*[b]	% *ee* (*endo*)[c]
1	TFA	r.t.	70	>99	95:05	50
2	HCl	r.t.	70	>99	70:30	90
3	HCl	r.t.	90	>99	86:14	90
4	HCl	-20 °C	90	50	92:7	93
5	HCl	-20 °C	120	>99	92:7	93
6	HBr	r.t.	70	95	82:18	65
7	$HClO_4$	r.t.	70	>99	90:10	55
8	*p*-TsOH	r.t.	70	90	81:19	70
9	$EtSO_3H$	r.t.	70	50	nd	nd
10	ClAcOH	r.t.	70	45	nd	nd

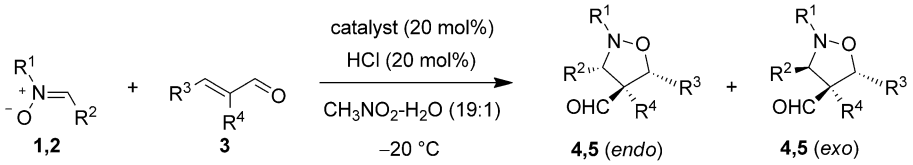
[a] The reactions were carried out using catalyst **A** (0.06 mmol), HX (0.06 mmol), nitrone (0.3 mmol), (*E*)-crotonaldehyde (1.2 mmol), CH_3NO_2 (3.8 mL), and H_2O (0.2 mL).
[b] Conversions and *endo*/*exo* ratios were determined by ^1H NMR analysis of the crude reaction mixtures.
[c] Product enantiomeric ratios were determined by HPLC using a Chiralcel ADV column after reduction of the aldehyde to alcohol with $NaBH_4$.

varying Brønsted acid component of the catalyst **MNP-A**. Using TFA as the salt, an excellent conversion (>99%) was achieved (entry 1, Table 1) and the desired isoxazolidine **4aa** was obtained with a high diastereoselectivity (*dr*, 95:05 *endo*/*exo*) at room temperature for 70 h. However, the enantioselectivity was in the non-satisfactory range of only 50%. Similarly, the cycloaddition proceeded smoothly using $HClO_4$, HBr, and *p*-TsOH derived catalysts of **MNP-A** to give high conversion and high *dr*, although a low enantiomeric excess of the major *endo* adduct was obtained (Table 1, entries 6–8). When the cycloaddition was carried out employing 20 mol% of HCl as a cocatalyst, the catalytic efficiency of **MNP-A** was significantly improved. The reaction proceeded with high conversion (>99%) under similar conditions at room temperature for 70 h and a high diastereoselectivity (70:30) and enantioselectivity (90%) were observed for the cycloadduct **4aa** (Table 1, entry 2).

The *dr* value was further improved with a longer reaction time (Table 1, entry 3). Superior levels of asymmetric induction and diastereocontrol was obtained using the HCl salt of **MNP-A** at −20 °C which afforded the isoxazolidine **4aa** in 93% *ee*, 92:7 *dr* and in greater than 99% conversion (Table 1, entry 5). Under the optimized reaction conditions, the homogeneous imidazolidinone **11** and the catalyst precursor **8** exhibited relatively low diastereo- and enantioselectivities of the desired isoxazolidines (entries 1 and 2, Table 2). This may be attributed to the high surface areas and small size of magnetite nanoparticles, which are more accessible to the reactants compared to homogeneous counterparts. The heterogeneous imidazolidinone **MNP-B** (entry 4, Table 2) exhibited comparable yield, diastereoselectivity and enantioselectivity as **MNP-A** (entry 3, Table 2). Since **MNP-A** was easily accessible using a convergent synthetic procedure with comparable loading as **MNP-B**, the scope of the reaction using various nitrones was surveyed using **MNP-A** at −20 °C.

As illustrated in Table 2, an array of functionalized *N*-methyl- and *N*-benzyl-substituted nitrones underwent effective cycloaddition to afford the desired isoxazolidines **4** and **5** in high yields and good to excellent diastereoselectivities and enantioselectivities (Table 2). The reaction took place smoothly with crotonaldehyde **3a** (entries 1–9 and entries 18–20) and acrolein **3b** (entries 10–12) as dipolarophiles to afford the desired isoxazolidines in high yields with good to excellent diastereoselectivity and enantioselectivity (62–96% yield, 80:20 to 93:7 *endo*:*exo*, 82–95% *ee*). As anticipated, we observed some limitations in this asymmetric 1,3-dipolar cycloaddition. The reaction of methacrolein (**3e**) with *N*-benzylidenebenzylamine *N*-oxide (**1a**) was found to be sluggish at −20 °C (entry 15). However, when the reaction mixture was stirred at room temperature, the desired product **4ae** was obtained in moderate yield (51%) and selectivity (70:30 *endo*:*exo*, 56% *ee*). No reaction was observed with sterically crowded aldehydes such as (*E*)-4-phenylbut-2-enal (**3c**), cinnamaldehyde (**3d**) and (*E*)-2-methylpent-2-enal (**3f**) at room temperature or at 80 °C (entries 13, 14 and 17).

Table 2. Application of the catalyst for 1,3-dipolar cycloadditions between different nirones and α,β-unstaurated aldehydes.[a]



Entry	Nitrones	Aldehydes	Cat.	Time [h]	Yield[b] [%]	*dr* *endo*:*exo*[c]	% *ee* (*endo*)[d]
1	**1a**, R^1 = Bn, R^2 = Ph	**3a**, R^3 = Me, R^4 = H	**8**	101	**4aa**, 93	84:16	87
2	**1a**, R^1 = Bn, R^2 = Ph	**3a**, R^3 = Me, R^4 = H	**11**	111	**4aa**, 91	84:16	80
3	**1a**, R^1 = Bn, R^2 = Ph	**3a**, R^3 = Me, R^4 = H	**MNP-A**	120	**4aa**, 96	92:7	93
4	**1a**, R^1 = Bn, R^2 = Ph	**3a**, R^3 = Me, R^4 = H	**MNP-B**	120	**4aa**, 95	90:10	90
5	**1b**, R^1 = Bn, R^2 = 4-BrC_6H_4	**3a**, R^3 = Me, R^4 = H	**MNP-A**	118	**4ba**, 86	86:14	93
6	**1b**, R^1 = Bn, R^2 = 4-BrC_6H_4	**3a**, R^3 = Me, R^4 = H	**MNP-B**	110	**4ba**, 85	85:15	86
7	**1c**, R^1 = Bn, R^2 = 4-ClC_6H_4	**3a**, R^3 = Me, R^4 = H	**MNP-A**	120	**4ca**, 80	95:5	94
8	**1d**, R^1 = Bn, R^2 = 4-MeC_6H_4	**3a**, R^3 = Me, R^4 = H	**MNP-A**	120	**4da**, 89	93:7	94
9	**1e**, R^1 = Bn, R^2 = 4-MeOC_6H_4	**3a**, R^3 = Me, R^4 = H	**MNP-A**	111	**4ea**,90	90:10	92
10	**1a**, R^1 = Bn, R^2 = Ph	**3b**, R^3 = H, R^4 = H	**MNP-A**	120	**4ab**,75	86:14	85
11	**1b**, R^1 = Bn, R^2 = 4-BrC_6H_4	**3b**, R^3 = H, R^4 = H	**MNP-A**	112	**4bb**, 65	85:15	90
12	**1c**, R^1 = Bn, R^2 = 4-ClC_6H_4	**3b**, R^3 = H, R^4 = H	**MNP-A**	110	**4bc**, 73	80:20	82
13	**1a**, R^1 = Bn, R^2 = Ph	**3c**, R^3 = $PhCH_2$, R^4 = H	**MNP-A**	120	–	–	–
14	**1a**, R^1 = Bn, R^2 = Ph	**3d**, R^3 = Ph, R^4 = H	**MNP-A**	120	–	–	–
15	**1a**, R^1 = Bn, R^2 = Ph	**3e**, R^3 = H, R^4 = Me	**MNP-A**	120	**4ae**, 10	–	–
16	**1a**, R^1 = Bn, R^2 = Ph	**3e**, R^3 = H, R^4 = Me	**MNP-A**	96[e]	**4ae**, 51	70:30	56
17	**1a**, R^1 = Bn, R^2 = Ph	**3f**, R^3 = Et, R^4 = Me	**MNP-A**	120	–	–	–
18	**2a**, R^1 = Me, R^2 = Ph	**3a**, R^3 = Me, R^4 = H	**MNP-A**	120	**5aa**, 62	92:8	95
19	**2b**, R^1 = Me, R^2 = 4-Cl C_6H_4	**3a**, R^3 = Me, R^4 = H	**MNP-A**	120	**5ba**, 73	86:14	94
20	**2c**, R^1 = Me, R^2 = 4-MeC_6H_4	**3a**, R^3 = Me, R^4 = H	**MNP-A**	115	**5ca**, 75	87:13	94

[a] See experimental procedures.
[b] Isolated yield.
[c] The *endo*/*exo* ratio was determined by ^{1}H NMR analysis of crude reaction mixture.
[d] The enantiomeric excess was determined by chiral HPLC analysis.
[e] The reaction was performed at room temperature.

Next we have evaluated the reusability of **MNP-A** in the 1,3-dipolar cycloaddition of *N*- benzylideneben-zylamine *N*-oxide (**1a**) with (*E*)-crotonaldehyde (**3a**) (see the Supporting Information).The recovery of **MNP-A** catalyst is achieved quantitatively by magnetic separation and it was successfully reused for 4 times with no substantial decrease in yield (yield from 94% to 89%) and with no appreciable decrease of diastereo- and enantiocontrol, affording *endo* isomers with enantioselectivity always higher than 89% (Supporting Information, Table S1). The TEM image of the recovered catalyst after 5 cycles reveals that the catalyst maintains its nanospheric dimensions with an average diameter of 13 nm (Figure 1c and the Supporting Information).

In conclusion, we have developed a new MNP supported imidazolidinone catalyst which was used for the first time for an asymmetric 1,3 dipolar cycloaddition of various nitrones with α,β-unsaturated aldehydes. The desired isoxazolidines were obtained in high yields with excellent *endo* diastereoselectivity and enantioselectivity. The results are comparable with those reported for imidazolidinones as reaction catalyst. Moreover the catalyst could be magnetically recovered and recycled for four times without any significant loss in yields and enantioselectivities of the *endo* adducts. The catalyst should find versatile applications in several catalytic reactions.

Experimental Section

General Procedure for the 1,3-Dipolar Cycloaddition using MNP-A

To a solution of the **MNP-A** (0.06 mmol) in CH_3NO_2 (3.8 mL) was added 0.3 N HCl (0.2 mL, 0.06 mmol). The mixture was stirred at room temperature for 10 min and then cooled to −20 °C. Then nitrone **1** or **2** (0.3 mmol) and aldehyde **3** (1.2 mmol) were added to the flask with stirring. Additional aldehyde **3** (0.9 mmol × 3) was added to the reaction mixture at 24 h intervals until the specified reaction time was reached. The catalyst **MNP-A** was removed from the reaction mixture using an external magnet. The resulting solution was evaporated under vacuum and purified by

silica gel column chromatography to afford the desired product **4** and **5**. The recovered catalyst was washed three times with MeOH, followed by CH_2Cl_2 and dried under vacuum, and was then reused for recycling experiments (Supporting Information, Table S1).

Supporting Information

Experimental procedures, characterization data of compounds, FT-IR, PXRD data, TEM images, recycling of the catalyst, the copies of ^{1}H NMR and ^{13}C NMR spectra and HPLC analysis spectra are available in the Supporting Information.

Acknowledgements

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